APR 15 2004
PATENT & TRADEMARK OFFICE

EXPRESS MAIL NO.: EL615431405US
Date Mailed: April 15, 2004

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	
Richard MURRAY, *et al.*	Art Unit: 1642
Appl. No. 10/021,660	Examiner: Nickol, Gary B.
Filed: December 6, 2001	Atty. Docket: 05882.0159.CNUS02
For: **NOVEL METHODS OF DIAGNOSIS OF ANGIOGENESIS, COMPOSITIONS AND METHODS OF SCREENING FOR ANGIOGENESIS MODULATORS**	Confirmation No. 5788

RESPONSE TO ELECTION/RESTRICTIONS

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22213-1450

Sir:

This is in response to the Office Action dated **March 24, 2004**, and is submitted on or before the due date of **April 24, 2004**. The Response includes amendments to the claims, as well as the remarks and amendments originally presented in the response submitted on January 20, 2004. The Examiner is requested to enter the amendments and consider the application.

The U.S. Patent and Trademark Office is hereby authorized to charge payment of any other fees associated with this communication or credit any overpayment to Deposit Account No. 08-3038 referencing docket number 05882.0159.CNUS02. A duplicate copy of this Response is attached.

THE AMENDMENTS

In the Specification:

Amend the paragraph starting at page 1, line 7:

The present application is a continuation-in-part (CIP) of co-pending United States Patent Application No. 09/637,977 ~~"Novel Methods of Diagnosis of Angiogenesis, Compositions And Methods of Screening For Angiogenesis Modulators", Attorney Docket No. A65110-1,~~ filed on August 11, 2000, which claims the benefit of priority to U.S.S.N. 60/148,425 filed August 11, 1999, both of which are incorporated herein by reference.

Amend the paragraph starting at page 6, line 5:

The terms "identical" or percent "identity," in the context of two or more nucleic acids or polypeptide sequences, refer to two or more sequences or subsequences that are the same or have a specified percentage of amino acid residues or nucleotides that are the same (i.e., about 70% identity, preferably 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or higher identity over a specified region (e.g., SEQ ID NOS:1-4), when compared and aligned for maximum correspondence over a comparison window or designated region) as measured using a BLAST or BLAST 2.0 sequence comparison algorithms with default parameters described below, or by manual alignment and visual inspection ~~(see, e.g., NCBI web site http://www.ncbi.nlm.nih.gov/BLAST/ or the like)~~. Such sequences are then said to be "substantially identical." This definition also refers to, or may be applied to, the compliment of a test sequence. The definition also includes sequences that have deletions and/or additions, as well as those that have substitutions. As described below, the preferred algorithms can account for gaps and the like. Preferably, identity exists over a region that is at least about 25 amino acids or nucleotides in length, or more preferably over a region that is 50-100 amino acids or nucleotides in length.

Amend the paragraph starting at page 7, line 7:

A preferred example of algorithms that is suitable for determining percent sequence identity and sequence similarity include the BLAST and BLAST 2.0 algorithms, which are described in Altschul, *et al.*, *Nuc. Acids Res.* 25:3389-3402 (1977) and Altschul, *et al.*, *J. Mol.*

Biol. 215:403-410 (1990). BLAST and BLAST 2.0 are used, with the parameters described herein, to determine percent sequence identity for the nucleic acids and proteins of the invention. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information ~~(http://www.ncbi.nlm.nih.gov/)~~. This algorithm involves first identifying high scoring sequence pairs (HSPs) by identifying short words of length W in the query sequence, which either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighborhood word score threshold (Altschul *et al.*, *supra*). These initial neighborhood word hits act as seeds for initiating searches to find longer HSPs containing them. The word hits are extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Cumulative scores are calculated using, e.g., for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always > 0) and N (penalty score for mismatching residues; always < 0). For amino acid sequences, a scoring matrix is used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T, and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, an expectation (E) of 10, M=5, N=-4 and a comparison of both strands. For amino acid sequences, the BLASTP program uses as defaults a wordlength of 3, and expectation (E) of 10, and the BLOSUM62 scoring matrix (see Henikoff and Henikoff, *Proc. Natl. Acad. Sci. USA* 89:10915-919(1989)) alignments (B) of 50, expectation (E) of 10, M=5, N=-4, and a comparison of both strands.

Amend the paragraph starting at page 8, line 18:

A "host cell" is a naturally occurring cell or a transformed cell that contains an expression vector and supports the replication or expression of the expression vector. Host cells may be cultured cells, explants, cells *in vivo*, and the like. Host cells may be prokaryotic cells such as *E. coli*, or eukaryotic cells such as yeast, insect, amphibian, or mammalian cells such as CHO, HeLa, and the like (see, *e.g.*, the American Type Culture catalog or web site~~, www.atcc.org~~).

Amend the paragraph starting at page 21, line 17:

In a preferred embodiment, angiogenesis sequences are those that are up-regulated in angiogenesis disorders; that is, the expression of these genes is higher in the disease tissue as compared to normal tissue. "Up-regulation" as used herein often means at least about a two-fold change, preferably at least about a three fold change, with at least about five-fold or higher being preferred. All accession numbers herein are for the GenBank sequence database and the sequences of the accession numbers are hereby expressly incorporated by reference. GenBank is known in the art, see, *e.g.*, Benson, DA, et al., Nucleic Acids Research 26:1-7 (1998) ~~and http://www.ncbi.nlm.nih.gov/~~. Sequences are also available in other databases, *e.g.*, European Molecular Biology Laboratory (EMBL) and DNA Database of Japan (DDBJ). In addition, most preferred genes were found to be expressed in a limited amount or not at all in heart, brain, lung, liver, breast, kidney, prostate, small intestine and spleen.

Amend the paragraph starting at page 28, line 8:

Transmembrane proteins may contain from one to many transmembrane domains. For example, receptor tyrosine kinases, certain cytokine receptors, receptor guanylyl cyclases and receptor serine/threonine protein kinases contain a single transmembrane domain. However, various other proteins including channels and adenylyl cyclases contain numerous transmembrane domains. Many important cell surface receptors such as G protein coupled receptors (GPCRs) are classified as "seven transmembrane domain" proteins, as they contain 7 membrane spanning regions. Characteristics of transmembrane domains include approximately 20 consecutive hydrophobic amino acids that may be followed by charged amino acids. Therefore, upon analysis of the amino acid sequence of a particular protein, the localization and number of transmembrane domains within the protein may be predicted (see, e.g., PSORT web site ~~http://psort.nibb.ac.jp/~~).

Amend the paragraph starting at page 30, line 7:

In addition, the angiogenesis nucleic acid sequences of the invention, e.g., the sequence in Table 1, are fragments of larger genes, *i.e.*, they are nucleic acid segments. "Genes" in this

context includes coding regions, non-coding regions, and mixtures of coding and non-coding regions. Accordingly, as will be appreciated by those in the art, using the sequences provided herein, extended sequences, in either direction, of the angiogenesis genes can be obtained, using techniques well known in the art for cloning either longer sequences or the full length sequences; see Ausubel, *et al.*, *supra*. Much can be done by informatics and many sequences can be clustered to include multiple sequences corresponding to a single gene, *e.g.*, systems such as UniGene ~~(see, http://www.ncbi.nlm.nih.gov/UniGene)~~.

Amend the paragraph starting at page 33, line 27:

In some embodiments, a TaqMan based assay is used to measure expression. TaqMan based assays use a fluorogenic oligonucleotide probe that contains a 5' fluorescent dye and a 3' quenching agent. The probe hybridizes to a PCR product, but cannot itself be extended due to a blocking agent at the 3' end. When the PCR product is amplified in subsequent cycles, the 5' nuclease activity of the polymerase, *e.g.*, AmpliTaq, results in the cleavage of the TaqMan probe. This cleavage separates the 5' fluorescent dye and the 3' quenching agent, thereby resulting in an increase in fluorescence as a function of amplification (*see*, for example, literature provided by Perkin-Elmer~~, *e.g.*, www2.perkinelmer.com~~).

In the Claims

1. (Currently Amended) A method of detecting an angiogenesis-associated transcript in an individual ~~cell of a patient~~, the method comprising: ~~contacting a biological sample from the patient with a polynucleotide that selectively hybridized to a sequence at least 80% identical to SEQ ID NO: 41~~

   a) determining the expression of a gene of SEQ ID NO: 41 in a first tissue of a first individual;

   b) comparing the expression of said gene in the first tissue sample to expression of said gene from a second tissue with no angiogenesis activity;

   wherein a higher level of expression in the first tissue sample indicates angiogenesis associated activity in said first individual.

2. (Currently Amended) The method of claim 1, wherein the second tissue is from said first individual ~~biological sample is a tissue sample~~.

3. (Currently Amended) The method of claim 1, wherein the first or second tissue ~~biological sample~~ comprises isolated nucleic acids.

4. (Original) The method of claim 3, wherein the nucleic acids are mRNA.

5. (Currently Amended) The method of claim 3, further comprising the step of amplifying said nucleic acids ~~before the step of contacting the biological sample with the polynucleotide~~.

6. (Currently Amended) The method of claim 1, wherein determining the expression of the gene further comprises contacting a polynucleotide complementary to SEQ ID NO:41 with said first or second tissue sample ~~comprises a sequence as shown in Table 1~~.

7. (Currently Amended) The method of claim ~~1~~[[6]], wherein the polynucleotide is labeled.

8. (Original) The method of claim 7, wherein the polynucleotide is labeled by a fluorescent label.

9. (Currently Amended) The method of claim ~~1~~[[6]], wherein the polynucleotide is immobilized on a solid surface.

10. (Currently Amended) The method of claim 1, wherein ~~the patient~~ said first individual is undergoing a therapeutic regimen to treat a disease associated with angiogenesis.

11. (Currently Amended) The method of claim 1, wherein ~~the patient~~ said first individual is suspected of having cancer.

12. (Withdrawn) An isolated nucleic acid molecule consisting of a polynucleotide sequence as shown in Table 1.

13. (Withdrawn) The nucleic acid molecule of claim 12, which is labeled.

14. (Withdrawn) The nucleic acid of claim 13, wherein the label is a fluorescent label.

15. (Withdrawn) An expression vector comprising the nucleic acid of claim 12.

16. (Withdrawn) A host cell comprising the expression vector of claim 15.

17. (Withdrawn) An isolated nucleic acid molecule which encodes a polypeptide having an amino acid sequence as shown in Table 2.

18. (Withdrawn) An isolated polypeptide which is encoded by a nucleic acid molecule having polynucleotide sequence as shown in Table 1.

19. (Withdrawn) An isolated polypeptide having an amino acid sequence as shown in Table

2.

20. (Withdrawn) An antibody that specifically binds a polypeptide of claim 18.

21. (Withdrawn) The antibody of claim 20, further conjugated to an effector component.

22. (Withdrawn) The antibody of claim 21, wherein the effector component is a fluorescent label.

23. (Withdrawn) The antibody of claim 21, wherein the effector component is a radioisotope.

24. (Withdrawn) The antibody of claim 20, which is an antibody fragment.

25. (Withdrawn) The antibody of claim 20, which is a humanized antibody.

26 (Withdrawn) A method of detecting a cell undergoing angiogenesis in a biological sample from a patient, the method comprising contacting the biological sample with an antibody of claim 20.

27. (Withdrawn) The method of claim 26, wherein the antibody is further conjugated to an effector component.

28. (Withdrawn) The method of claim 27, wherein the effector component is a fluorescent label.

29. (Withdrawn) The method of detecting antibodies specific to angiogenesis in a patient, the method comprising contacting a biological sample from the patient with a polypeptide comprising a sequence as shown in Table 2.

REMARKS

Claims 1-11 are pending in this application.

The Amendments

The amendments in Claims 1-3 and 5 are supported, for example, by page 21, lines 17-21; page 33, lines 17-26; page 49, lines 5-18; and page 50, lines 4-11. The amendments in Claim 6 are supported, for example, by former Claim 6 and by page 11, lines 9-22. The amendments in Claims 10-11 are supported, for example, by page 49, lines 5-18, and page 50, lines 4-11.

No new matter is added in the amendments. The Examiner is respectfully requested to enter the amendments.

The Response

The Examiner alleges that the amendments filed on January 21, 2004 are not readable on the elected invention. Applicants submit the above amendments in order to comply with the Examiner's rejection. For the Examiner's convenience, the remarks and amendments to the specification accompanying the amendments filed on January 21, 2004 are included herein. The Examiner is respectfully requested to enter the amendments.

Objections to Oath/Declaration

The Oath/Declaration filed on December 6, 2001 is objected to by the Examiner because the signature of Richard Murray is not dated. Applicants have attached herewith a new Oath/Declaration with Richard Murray's signature dated. Therefore, the objection to the Oath/Declaration should be withdrawn.

Objections to Priority

The Applicant's claims to priority in the instant application are objected to by the Examiner because the parent applications allegedly do not lend support for disclosure of SEQ ID NO:41. Applicants respectfully traverse this objection.

The instant application claims priority to U.S. Patent Application No. 09/637,977 (referred to as Attorney Docket No. A65110-1 on page 1 of the instant specification), which claims the benefit of U.S. Provisional Patent Application No. 60/148,425, filed August 11, 1999.

The Examiner contends that there is allegedly no disclosure in the parent applications to show that the sequence disclosed in SEQ ID NO:41 in the instant application was present in the parent applications. Applicants respectfully disagree with this contention.

As known by those of ordinary skill in the art, and as provided by U.S. Application Nos. 09/637,977 and 60/148,425, accession numbers are readily accessed through National Center for Biotechnology Information Genbank's website. *See* http://www.ncbi.nlm.nih.gov/Genbank/index.html. Both U.S. Application Nos. 09/637,977 and 60/148,425, contain references to BMX in Tables 1-5 in U.S. Patent Application No. 09/637,977, and in Table 1 of application No. 60/148,425. Specifically, the tables of the referenced parent applications contain information to obtain the sequence information for BMX through its Genbank Accession Number X83107. When querying Genbank for accession number X83107, a 2456 bp sequence is pulled from the database (copy of Genbank sequence enclosed herewith as Exhibit A). In addition, one of ordinary skill in the art would have had access to this sequence since the Genbank submission date, listed in Exhibit A as August 22, 1995, before the parent application priority date.

Thus, those of ordinary skill in the art, guided by the disclosure provided in the parent application, would know where to find the sequence contained within Genbank Accession No. X83107. Moreover, one of ordinary skill in the art, guided by the instant specification, could perform a comparison between the sequence disclosed in accession number X83107 and the nucleic acid sequence disclosed in SEQ ID NO:41 in the instant application and show that there is indeed complimentary identification between the sequence comprising SEQ ID NO:41 and the sequence disclosed in accession number X83107. Therefore, the priority information stating the accession number is identical to the sequence disclosed in the instant application, and as such one of ordinary skill in the art would have known that the inventors had possession of SEQ ID NO:41 at the time of filing and disclosure of Genbank Accession No. X83107 in the parent application of August 11, 1999.

To conclude, the information disclosed in SEQ ID NO:41 is identical to the information disclosed in the referenced parent applications through the Genbank Accession No. X83107. The objections to the priority information should therefore be withdrawn, and a priority date of August 11, 1999 recognized.

Objections to Disclosure

Claim 1 is objected to by the Examiner for reciting the language "A method of detecting angiogenesis-associated transcript." The Examiner states that such language is allegedly grammatically unclear. Applicant has amended the claim to make the phrase grammatically correct by adding the term "an" before "angiogenesis-associated transcript. The objection to Claim 1 should therefore be removed.

Claim 1 is also objected to because claim 1 is allegedly unclear for reciting a term in the past tense. Applicants have removed the term "that selectively hybridized". The objections to Claim 1 should be withdrawn.

Claim 6 is objected to by the Examiner for being of improper dependent form for allegedly failing to further limit the subject matter of a previous claim. This objection is rendered moot by the cancellation of Claim 6.

35 U.S.C. §112 First Paragraph Rejection, Written Description

Claims 1-11 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection to the claims is overcome in view of the amendments and Applicant's remarks below.

Applicants have amended Claim 1 to remove the term "at least 80% identical". The claim now reads "determining the expression of a gene encoding an amino acid sequence of SEQ ID NO:41".

Therefore, the § 112 first paragraph rejection of Claims 1-11 should be withdrawn.

35 USC §102 Rejections

Au-Young et al.

Claims 1-11 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Au-Young et al. (U.S. Patent No. 6,500,938). The rejection to the claims is overcome in view of the amendments.

Claim 1 has been amended to detect angiogenesis by first detecting the expression of

SEQ ID NO:41 in a first tissue sample of an individual, then comparing the expression in the first sample to the expression levels in a normal tissue in order to determine if the first tissue is undergoing angiogenesis.

In contrast, Au-Young et al. does not disclose a method for detecting angiogenesis in a first tissue sample by comparing the expression level of the nucleic acid of SEQ ID NO:41 to the expression level in normal tissue. On the contrary, Au-Young discloses only an array system comprising DNA probes on a microarray. Instead, Au-Young discloses, as the Examiner has noted, the detection of a "complex" upon binding of nucleic acids onto the polynucleotides anchored onto the array. Au-Young does not detect the presence of a nucleic acid in two tissues in order to determine if an individual has angiogenesis by comparing the levels of expression in a tissue sample with that of normal tissue that is not undergoing angiogenesis.

Au-Young in fact teaches away from the instant application by disclosing the use of single microarrays comprising a plurality of polynucleotides attached to the surface of the microarray. Because a tissue sample added to the microarray is exposed to the entire array, only one sample at a time can be tested in the array. Therefore, the invention disclosed in Au-Young can only test one sample at a time, not compare the expression levels of two samples against the same gene. This is in complete accordance with the objectives of the Au-Young invention of comparing the expression levels of a plurality of targets simultaneously to correlate the expression pattern of a *plurality of genes* with a particular disease or condition. See '938 patent, col. 4, lines 34-39.

Moreover, Au-Young does not disclose information regarding transcripts important in the process of angiogenesis. Au-Young merely discloses a generic means of determining polynucleotides suitable for anchoring onto a microchip array surface. Au-Young does not disclose any information regarding genes important in angiogenesis, or the growth of blood vessels.

Because Au-Young does not disclose a method of detecting angiogenesis by comparing a tissue sample to that of a normal tissue sample not undergoing angiogenesis, the reference does not anticipate the instant application. Therefore, the rejection should be withdrawn.

Ekman et al.

Claims 1, and 3-7 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Ekman et al. (U.S. Patent Application No. 2002/0173481). The rejection to the claims is overcome in view of the amendments.

Claim 1 has been amended to detect angiogenesis by first detecting the expression of SEQ ID NO:41 in a first tissue sample of an individual, then comparing the expression in the first sample to the expression levels in a normal tissue in order to determine if the first tissue is undergoing angiogenesis.

In contrast, Ekman teaches a method of treating or preventing arteriostenosis, a process significantly different from angiogenesis. Angiogenesis is the process involving the generation of new blood vessels (see page 1, lines 22-23 of the instant application). In contrast, arteriostenosis is the process whereby the arterial lumen undergoes a narrowing process, involving inflammatory processes and the like mediated through BMX tyrosine kinase activity. See Ekman et al., paragraph 0014. Because BMX appears to mediate and stimulate the inflammatory processes important to arteriostenosis, Ekman seeks to regulate BMX associated tyrosine kinase activity. See Ekman et al., paragraph 0018.

In contrast, the instant application seeks not to regulate BMX associated tyrosine kinase activity for the purposes of inhibiting the process of arteriostenosis. Instead, the instant application seeks to detect the expression of BMX (SEQ ID NO:41) in order to detect if an individual is undergoing angiogenesis. Therefore, quantification of expression levels through the comparison of a tissue sample with a sample known not to undergo angiogenesis is important to the instant application. Ekman does not disclose the use of quantifying expression levels of BMX in order to detect the process of angiogenesis. Instead, Ekman discloses the use of assays "known in the art for detecting *mutations or gene defects or abnormalities* may be used, such as restriction digests, PCR assays ...Northern blotting, hybridization of labeled oligonucleotides to the gene..." See paragraph 0021 (emphasis added). Thus, Ekman's disclosure is inapposite to the instant application because it seeks to detect "gene defects or abnormalities" variants, and not the BMX gene itself.

Because Ekman does not disclose a method of detecting angiogenesis by comparing a tissue sample to that of a normal tissue sample not undergoing angiogenesis, but instead discloses a method for detecting arteriostenosis, the reference does not anticipate the instant

application. Therefore, the rejection should be withdrawn.

Kaukonen et al.

Claims 1-7 and 10 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Kaukonen et al. (British Jnl. Haematology, 1996, Vol. 94, pages 455-460), and as allegedly further evidenced by Padro et al. (Blood, April 2000, Vol. 95(8), abstract). The rejection is overcome in view of the amendments.

Claim 1 has been amended to detect angiogenesis by first detecting the expression of SEQ ID NO:41 in a first tissue sample of an individual, then comparing the expression in the first sample to the expression levels in a normal tissue in order to determine if the first tissue is undergoing angiogenesis.

Kaukonen discloses the detection of BMX in fractionated normal leukocytes and cord blood cells to investigate its possible role in the differentiation of hematopoietic cells. See pg. 455. Although Kaukonen does not disclose a method of detecting angiogenesis, the Examiner states that the "BMX sequence assayed by Kaukonen et al ... would inherently have the feature of being associated with angiogenesis." Applicants respectfully disagree with the Examiner. Angiogenesis is a process by which new blood vessels are formed, and is commonly associated with embryonic development. See page 1, lines 22-23 of the instant application. The process occurs in several stages, including endothelial cell protease production, migration of cells, and proliferation. Later stages of angiogenesis include remodeling, and the population of vessels with mural cells. See pages 1-2 of the instant application. The process of angiogenesis, therefore, does not comprise only leukocytes, cord blood cells or other hematopoietic cell types, as is studied in Kaukonen. The process includes many different cellular types.

Thus, it is incorrect to maintain that BMX expression in isolated hematopoietic cells would inherently speak to angiogenesis. One of ordinary skill in the art, instead, would know that the isolation and analysis of hematopoietic cells could not tell a practitioner if angiogenesis is occurring. Kaukonen, therefore, does not teach or anticipate the instant application because a practitioner cannot detect angiogenesis by looking at isolated hematopoietic cells.

Adding the reference of Padro et al. does not cure the deficiencies in Kaukonen. Padro only speaks to the presence of increased angiogenesis in the bone marrow of patients with

leukemia. Padro looks at physical manifestations of angiogenesis only, by detecting microvessel formation within the bone marrow tissue itself. Kaukonen, in contrast, is not looking at the entire bone marrow tissue, which could support angiogenesis, but isolates only the leukocyte fraction of bone marrow cells in order to perform their BMX nucleic acid analysis. See page 456. Kaukonen, therefore, does not use "tissue" as one of ordinary skill in the art would understand, and is not comparable to the observations that Padro discloses.

Moreover, Kaukonen does not disclose the method of detecting angiogenesis by comparing the expression in one tissue versus tissue where angiogenesis is not occurring. Kaukonen does not disclose a method of detecting angiogenesis in a cell by detecting the expression of SEQ ID NO:41 in a tissue sample, and comparing the expression of SEQ ID NO:41 to a tissue sample where no angiogenesis is occurring.

Because Kaukonen, combined with Padro, does not disclose a method of detecting angiogenesis by comparing a tissue sample to that of a normal tissue sample not undergoing angiogenesis, but instead discloses a method for detecting arteriostenosis, the reference does not anticipate the instant application. Therefore, the rejection should be withdrawn.

35 U.S.C. § 103 Rejections

Combination of Kaukonen et al., Padro et al. and Au-Young et al.

Claims 1-11 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Kaukonen et al., as allegedly further evidenced by Padro et al., and allegedly further in view of Au-Young et al. The rejection is overcome in view of the amendments to the claims.

Claim 1 has been amended to detect angiogenesis by first detecting the expression of SEQ ID NO:41 in a first tissue sample of an individual, then comparing the expression in the first sample to the expression levels in a normal tissue in order to determine if the first tissue is undergoing angiogenesis.

Kaukonen discloses the detection of BMX in fractionated normal leukocytes and cord blood cells to investigate its possible role in the differentiation of hematopoietic cells. See pg. 455. Although Kaukonen does not disclose a method of detecting angiogenesis, the Examiner states that the "BMX sequence assayed by Kaukonen et al ... would inherently have the feature of being associated with angiogenesis." Applicants again respectfully disagree with the

Examiner. Angiogenesis is a process by which new blood vessels are formed, and is commonly associated with embryonic development. See page 1, lines 22-23 of the instant application. The process occurs in several stages, including endothelial cell protease production, migration of cells, and proliferation. Later stages of angiogenesis include remodeling, and the population of vessels with mural cells. See pages 1-2 of the instant application. The process of angiogenesis, therefore, does not comprise only leukocytes, cord blood cells or other hematopoietic cell types. The process includes many different cellular types.

Adding the reference of Padro et al. does not cure the deficiencies in Kaukonen. Padro only speaks to the presence of increased angiogenesis in the bone marrow of patients with leukemia. Padro looks at physical manifestations of angiogenesis only, by detecting microvessel formation within the bone marrow tissue itself. Kaukonen, in contrast, is not looking at the entire bone marrow tissue, which could support angiogenesis, but isolates only the leukocyte fraction of bone marrow cells in order to perform their BMX nucleic acid analysis. See page 456. Kaukonen, therefore, does not use "tissue" as one of ordinary skill in the art would understand, and is not comparable to the observations that Padro discloses.

Therefore, Padro teaches away from Kaukonen because it does not analyze isolated cells to detect angiogenesis. Padro uses the entire bone marrow tissue to detect angiogenesis. Combined with the definition of angiogenesis as a growth of new blood vessels involving the interaction of many different cell types, Kaukonen does not teach a method of angiogenesis.

Combining Au-Young does not cure the deficiencies of Kaukonen and Padro. Au-Young discloses an array system comprising DNA probes on a microarray. Au-Young does not teach a method of detecting angiogenesis by comparing expression levels in a tissue sample with that from a sample known not to undergo angiogenesis. Au-Young in fact teaches away from the instant application by disclosing the use of single microarrays comprising a plurality of polynucleotides attached to the surface of the microarray. Because a tissue sample added to the microarray is exposed to the entire array, only one sample at a time can be tested in the array. Therefore, the invention disclosed in Au-Young can only test one sample at a time, in contrast to the instant application which requires the testing of two tissue samples. This is in complete accordance with the objectives of the invention of comparing the expression levels of a plurality of targets simultaneously to correlated the expression pattern of a *plurality of nucleotides* with a

particular disease or condition, not to compare the expression pattern of the same gene in two distinct tissue samples. See '938 patent, col. 4, lines 34-39.

Because Kaukonen, combined with Padro and Au-Young, does not disclose a method of detecting angiogenesis by comparing a tissue sample to that of a normal tissue sample not undergoing angiogenesis, but instead discloses a method for detecting arteriostenosis, the instant application is not rendered obvious by the combination of the references. Therefore, the rejection should be withdrawn.

Combination of Ekman et al. and Au-Young et al.

Claims 1-9 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Ekman et al., and as allegedly further in view of Au-Young et al. The rejection is overcome in view of the amendments.

Claim 1 has been amended to detect angiogenesis by first detecting the expression of SEQ ID NO:41 in a first tissue sample of an individual, then comparing the expression in the first sample to the expression levels in a normal tissue in order to determine if the first tissue is undergoing angiogenesis.

In contrast, Ekman teaches a method of treating or preventing arteriostenosis, a process significantly different from angiogenesis. See above discussion. Ekman does not disclose the use of quantifying expression levels of BMX in order to detect the process of angiogenesis. Instead, Ekman discloses the use of assays "known in the art for detecting mutations or gene defects or abnormalities may be used, such as restriction digests, PCR assays ...Northern blotting, hybridization of labeled oligonucleotides to the gene..." See paragraph 0021. Thus, Ekman's disclosure is inapposite to the instant application because it seeks to detect "gene defects or abnormalities" variants, and not the non-mutated BMX gene itself.

Combining Au-Young does not cure the deficiencies present in Ekman. Au-Young discloses an array system comprising DNA probes on a microarray. Au-Young does not teach a method of detecting angiogenesis by comparing expression levels in a tissue sample with that from a sample known not to undergo angiogenesis. Au-Young in fact teaches away from the instant application by disclosing the use of single microarrays comprising a plurality of polynucleotides attached to the surface of the microarray. Because a tissue sample added to the

microarray is exposed to the entire array, only one sample at a time can be tested in the array. Therefore, the invention disclosed in Au-Young can only test one sample at a time, in contrast to the instant application which requires the testing of two tissue samples. This is in complete accordance with the objectives of the invention of comparing the expression levels of a plurality of targets simultaneously to correlate the *expression pattern* of a plurality of nucleotides with a particular disease or condition, not to compare the expression pattern of the same gene in two distinct tissue samples. See '938 patent, col. 4, lines 34-39.

Because Ekman, combined with Au-Young, does not disclose a method of detecting angiogenesis by comparing a tissue sample to that of a normal tissue sample not undergoing angiogenesis, but instead discloses a method for detecting arteriostenosis, the instant application is not rendered obvious by the combination of the references. Therefore, the rejection should be withdrawn.

CONCLUSION

Applicants believe that the application is in good and proper condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned.

Respectfully submitted,

Date: April 15, 2004

Albert P. Halluin (Reg. No. 25,227)
Viola T. Kung (Reg. No. 41,131)
Lorelei P. Westin (Reg. No. 52,353)

HOWREY SIMON ARNOLD & WHITE, LLP
301 Ravenswood Avenue
Box 34
Menlo Park, CA 94025
Tel. (650) 463-8181